ciated with the risk of fatal or near-fatal attacks of asthma; the excessive use of albuterol was found to have a similar but weaker association.[15] A controlled study of the effects of the regular use of fenoterol versus placebo showed worsened asthma control with the active treatment.[16] Finally, several studies have shown that a regular use of β-agonists leads to the loss of their ability to protect against the bronchoconstriction provoked by methacholine, exercise, and antigen inhalation.[17]

The stakes in resolving the question of possibly harmful effects of the regular use of inhaled β-agonists have been raised by the introduction of salmeterol, a very-long-acting inhaled β-agonist, into the United States market. So far, fears that its use might lead to an increase in the frequency or severity of attacks of asthma seem unfounded, and two large studies comparing the regular use of salmeterol with the regular use of albuterol and of placebo not only show salmeterol to be most effective in improving asthma control but also fail to show any adverse effect of the regular use of albuterol versus placebo.[18,19] In patients with asthma inadequately controlled with the use of inhaled corticosteroids, the addition of twice-a-day inhalations of salmeterol has been shown to be superior to doubling the dose of the inhaled corticosteroid.[20]

The implications of the findings of basic research on the pathophysiology of asthma and of clinical research on asthma treatment are concordant. For patients with more than mild asthma, the regular use of an inhaled corticosteroid and the as-needed use of an inhaled β-agonist are effective and safe. Concerns over possible long-term toxicity of the systemic absorption of an inhaled corticosteroid seem unfounded, at least so long as the total dose of inhaled corticosteroid is less than 800 to 1,000 μg per day for adults and less than 400 μg per day for children. For patients inadequately controlled on standard doses of those medications, the addition of the regular use of salmeterol seems likely to be more effective than increasing the dose of the inhaled corticosteroid.

The major features of these recommendations for asthma treatment, described in detail by Kleerup and Tashkin in this issue,[21] have been endorsed by consensus groups and expert panels around the world. Their validity is not immutable. The results of large, ongoing prospective studies on the effects of regularly inhaled β-agonists or corticosteroids may cause a reassessment of their place in treatment. New inhaled corticosteroid preparations with greater local potency and less systemic absorption are about to be released,[22] and other, completely novel therapies with more precise mechanisms of action are under development. For the small proportion of asthmatic patients whose disease is not controlled by current treatments, the future holds hope. In the meantime, our obligation as a healing profession is to be certain that these patients understand the nature of their disease, the purposes of their treatments, the availability of tools for self-monitoring, and the instructions for seeking a higher level of care. This obligation, no less than the prescription of effective and safe medications, is properly emphasized in Kleerup and Tashkin's review.

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REFERENCES

1. Centers for Disease Control: Asthma—United States, 1980-1990. MMWR 1992; 41:733-735

2. Weiss KB, Gergen PJ, Hodgson TA: An economic evaluation of asthma in the United States. N Engl J Med 1992; 326:862-866

3. Dunnill MA: The Morphology of the Airways in Bronchial Asthma. Park Ridge, Ill, American College of Chest Physicians, 1975, pp 213-321

4. Laitinen LA, Heino M, Laitinen A, Kava T, Haahtela T: Damage of the airway epithelium and bronchial reactivity in patients with asthma. Am Rev Respir Dis 1985; 131:599-606

5. Wiggs BR, Bosken C, Paré PD, James A, Hogg JC: A model of airway narrowing in asthma and in chronic obstructive pulmonary disease. Am Rev Respir Dis 1992; 145:1251-1258

6. Robinson DS, Hamid Q, Ying S, et al: Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. N Engl J Med 1992; 326:298-304

7. Kay AB: Asthma and inflammation. J Allergy Clin Immunol 1991; 87:893-911

8. Brusselle GG, Kips JC, Joos G, Bluethmann H, Pauwels RA: Allergen-induced airway inflammation and bronchial responsiveness in wild-type and interleukin-4 deficient mice. Am J Respir Cell Mol Biol 1995; 12:254-259

9. Juniper EF, Kline PA, Vanzieleghem MA, Ramsdale EH, O'Byrne PM, Hargreave FE: Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. Am Rev Respir Dis 1990; 142:832-836

10. Haahtela T, Järvinen M, Kava T, et al: Comparison of a β_2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. N Engl J Med 1991; 325:388-392

11. Woolcock AJ, Yan K, Salome CM: Effect of therapy on bronchial hyperresponsiveness in the long-term management of asthma. Clin Allergy 1988; 18:165-176

12. Trigg CJ, Manolitsas ND, Wang J, et al: Placebo-controlled immunopathologic study of four months of inhaled corticosteroids in asthma. Am J Respir Crit Care Med 1994; 150:17-22

13. Haahtela T, Järvinen M, Kava T, et al: Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. N Engl J Med 1994; 331:700-705

14. Chervinsky P, van As A, Bronsky EA, et al: Fluticasone proprionate aerosol for the treatment of adults with mild to moderate asthma. J Allergy Clin Immunol 1994; 94:676-683

15. Spitzer WO, Suissa S, Ernst P, et al: The use of β-agonists and the risk of death and near death from asthma. N Engl J Med 1992; 326:501-506

16. Sears MR, Taylor DR, Print CG, et al: Regular inhaled β-agonist treatment in bronchial asthma. Lancet 1990; 336:1391-1396

17. O'Connor BJ, Aikman SL, Barnes PJ: Tolerance to the nonbronchodilator effects of inhaled β_2-agonists in asthma. N Engl J Med 1992; 327:1204-1208

18. Pearlman DS, Chervinsky P, LaForce C, et al: A comparison of salmeterol with albuterol in the treatment of mild-to-moderate asthma. N Engl J Med 1992; 327:1420-1425

19. D'Alonzo GE, Nathan RA, Henochowicz S, Morris RJ, Ratner P, Rennard SI: Salmeterol xinafoate as maintenance therapy compared with albuterol in patients with asthma. JAMA 1994; 271:1412-1416

20. Greening AP, Ind PW, Northfield M, Shaw G: Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid—Allen & Hanburys Limited UK Study Group. Lancet 1994; 344:219-224

21. Kleerup EC, Tashkin DP: Outpatient treatment of adult asthma. West J Med 1995; 163:49-63

22. Brattsand R, Thalén A, Roempke K, Källström L, Gruvstad E: Development of new glucocorticosteroids with a very high ratio between topical and systemic activities. Eur J Respir Dis [Suppl] 1982; 122:62-73

Sinusitis—Beginning a New Age of Enlightenment?

THE PARANASAL SINUSES were first described by Leonardo da Vinci in the publication "Two Views of the Skull." Since his description, numerous theories have been espoused on the anatomical or physiologic impor-

tance of the sinuses in humans. These include insulation, reducing cranial weight, heating and humidifying the air, imparting resonance to the voice, and simply to replace functionless bone. Despite the proliferation of theories, their functional role remains a mystery. Less mysterious to millions of patients is the misery associated with their diseased sinuses. In fact, some have argued that this evolutionary legacy has "proved much more of a liability than an asset as no other species has the misfortune to suffer from sinusitis or other allied respiratory problems."[1(p214)]

Although the function of the paranasal sinuses is unclear, our understanding of the epidemiology, pathophysiology, and treatment of sinusitis is advancing. As pointed out by Reuler and co-workers elsewhere in this issue, sinusitis is one of the most prevalent disorders encountered in general medical practice.[2] In the 1992 National Ambulatory Medical Survey, sinusitis was the fifth most common diagnosis for which an antibiotic was prescribed, an increase of almost 80% over three years previously.[3] Similarly, the 1992 National Health Review Survey showed that the prevalence rate for sinusitis (146 per 1,000 population) exceeded that of any other reported chronic condition.[4]

Why is sinusitis so prevalent, and why is its prevalence apparently increasing? It is tempting to speculate that the observed rise in prevalence is related to a rise in predisposing factors. For example, an increasing number of Americans are living in metropolitan areas characterized by poor air quality and nasal irritants. Further, higher population density is known to enhance the spread of infectious diseases such as viral rhinitis, a frequent antecedent of acute sinusitis. Alternatively, the rising prevalence of sinusitis may be more apparent than real and be related to better diagnostic modalities. Fiberoptic rhinoscopy allows direct visualization of diseased sinus mucosa, and its use may lead to an increased detection of occult or chronic diseases. Computed tomography (CT) and nuclear magnetic resonance imaging are much more sensitive to mucosal changes than standard "plain film" radiographs. In a recent investigation, 87% of subjects with community-acquired colds had CT evidence of maxillary sinusitis, findings that resolved spontaneously in most of the subjects. Therefore, CT may be too sensitive for the purpose of determining who needs treatment. In any case, an increased recognition of sinus disease, including subclinical cases, rather than an increased incidence of the disease, may explain the rising prevalence.

Whether a real phenomenon or simply an artifact of changing diagnostic technology, the surge in cases of sinus disease is associated with a large number of patient visits and increased health care expenditures. Each year, patients make 16 million physician visits and spend more than $2 billion on over-the-counter medications in pursuit of symptomatic relief of sinus disease. These statistics alone reflect the substantial morbidity of sinusitis. Despite the high prevalence of disease and its associated morbidity and health care costs, our knowledge base is meager as relatively few original investigations have been published on sinusitis in recent years. Further studies are needed to better define the epidemiology of acute sinusitis and to guide prevention strategies. Can acute sinusitis be prevented by using nasal corticosteroids to more aggressively manage allergic rhinitis? Is sinusitis averted by the prompt use of nasal decongestants for sufferers of the common cold? Should patients with viral rhinitis avoid the use of antihistamines (including scores of over-the-counter medications) that theoretically may predispose to sinusitis by thickening secretions and decreasing sinus drainage? All of these practical treatment issues need to be addressed in sound clinical investigations.

The diagnosis of sinusitis also needs attention. For acute sinusitis, the clinical evaluation has been shown sufficient for diagnosis in most patients. General internists diagnose acute sinusitis with about 75% accuracy, and a recent decision analysis suggests probability thresholds for empiric treatment or diagnostic testing. This decision strategy has not been validated, however, and should be examined to see if it improves patient outcomes. In the initial treatment of acute disease, therapeutic regimens that include antibiotics plus decongestants lead to good clinical response rates. Solitary studies on the role of ancillary therapies such as guaifenesin, niflumic acid (a nonsteroidal anti-inflammatory drug tested in Europe), and nasal corticosteroids suggest possible benefit, but further study is needed. Because the overall response rate is high, studies will be needed to determine if therapies reduce the intensity and duration of symptoms and should include long-term follow-up to assess relapse rates.

Although first-line therapy is effective for most primary care patients with acute sinusitis, 10% to 25% of patients have persistent symptoms that require a second course of therapy. For these patients, the most cost-effective diagnostic and therapeutic approach is yet to be determined. In my general medical practice, I confirm the diagnosis with a single Waters' view radiograph before prescribing an extended course of a broad-spectrum antibiotic plus decongestants. Others treat empirically or obtain a sinus CT to better examine the sinuses before treating further.

In population-based surveys, the prevalence of chronic sinusitis far exceeds that of acute sinusitis, and it is in this realm that some of the most important recent advances have been made. Sinus CT has increased greatly our understanding of the anatomic changes in chronic sinusitis and guided the development of new surgical interventions. It has shown that the ostiomeatal complex, an area at the confluence of drainage from the frontal, maxillary, and anterior ethmoid sinuses, is usually diseased in chronic sinusitis. Studies in animals have shown that poor sinus drainage is the seminal event that precipitates acute infection, and it is thought that the mucosal changes of chronic sinusitis are due to persistent obstruction. Functional endoscopic sinus surgery is directed at restoring physiologic sinus drainage by removing diseased mucosa in the ostiomeatal complex. Case series have shown a high response rate, although outcomes have not been

measured rigorously, and there are no randomized trials comparing this surgical therapy with aggressive medical management. Because endoscopic sinus operations are expensive and carry a small risk of serious complications, this unproved but promising treatment option deserves further study.

The evolutionary impetus behind the development of the paranasal sinuses may never be fully understood. But we are poised to enter a new age of enlightenment about the diagnosis and management of the diseased sinuses. Advanced imaging procedures, fiberoptic visualization, and an improved array of pharmacologic and surgical treatments should catalyze our understanding of sinus disorders. The important next step is to design and carry out clinical trials to determine how each of these resources is optimally used to improve patient outcomes in a cost-effective manner.

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REFERENCES

1. Evans PHR: The paranasal sinuses and other enigmas: An aquatic evolutionary theory. J Laryngol Otol 1992; 106:214-225

2. Reuler JB, Lucas LM, Kumar KL: Sinusitis: A review for generalists. West J Med 1995; 163:40-48

3. McCaig LF, Hughes JM: Trends in antimicrobial drug prescribing among office-based physicians in the United States. JAMA 1995; 273:214-219

4. Benson V, Marano MA: Current estimates from the National Health Interview Survey. Vital Health Stat [10] 1994; (189):1-269